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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,054	11/17/2000	Gerald R. Crabtree	STAN-166	7611

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EXAMINER
COOK, LISA V

ART UNIT	PAPER NUMBER
1641	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/716,054	Applicant(s) CRABTREE ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 16-39* is/are pending in the application.

4a) Of the above claim(s) *1-3 and 25-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3 and 16-39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicants' election of Group II – claims 16-24 with traverse is acknowledged. (See paper#15, filed 2/15/02). Applicant does not traverse the Restriction Requirement on the grounds of lack of patentable distinctness. The traversal on the ground(s) "that the examiner has not shown that a serious burden would be required to examine all of the claims", is not found convincing.

This is not found persuasive because MPEP § 808.02 recites:

> Where related inventions as claimed are shown to be distinct under the criteria of MPEP § 806.05(c)- § 806.05(i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof, (B) A separate status in the art when they are classified together, or (C) A different field of search.

In the instant case, (A) -The Restriction Requirement under 35 U.S.C. § 121 in Paper #14 mailed 12/10/01 established distinctness of the inventions and separate classification thereof:

(B) The inventions of Groups I, II, and III would require a separate status in the art when they are classified together; the invention as a whole is drawn to a non-naturally occurring bifunctional molecule having therapeutic utility. Such inventions are classified in 530, subclass 300 or 350 for example.

(C) With respect to a different field of search – Because these inventions are distinct and have acquired separate status in the art as shown by their different classification, recognized divergent subject matter and because the search required for each invention is not substantially coextensive with the search required for the remaining invention, restriction for examination purposes as indicated is proper. Please note that the classifications in the restriction are illustrative only and do **not** represent all the classes and subclasses, which must be searched for each invention; nor is the search limited to issued US patents, but rather includes published foreign patents and applications as well as literature search.

2. Further, the combination of Groups II and III (claims 16-24 and 27-39) for examination on the merits is deemed incorrect. The merging of these groups would combine patentably distinct inventions. Although Group III is directed to a specific species of the genus of the claims of Group II. Group III includes limitations that are not required to search the genus claims. Namely Group III requires a linking group with the particular formula Z-L-X, which in not required for claims 16-24 Group II. Therefore the inventions were not rejoined.

3. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1-3 and 27-39 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The Restriction Requirement is still deemed proper and is therefore made **FINAL.**

OBJECTIONS WITHDRAWN

Specification

Applicant has corrected the following noted objection in the amendment filed 10/9/01 in paper #12. The following objections are obviated:

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. The disclosure is objected to because page 6, line 35 and page 13, lines 30-33 – list numbers that appear to be U.S. Patent numbers. However the specification does not clearly identify the numbers as such, therefore they could be foreign application numbers, reference identification numbers, etc. Please add "U.S. Patent No." Correction is required. See MPEP § 608.01(b).

OBJECTIONS MAINTAINED

Applicant has not responded to the following objections. Therein the objections are maintained.

Drawings

6. This application has been filed with informal drawings. Formal drawings are required in reply to the Office action to avoid abandonment of the application. Drawing corrections will not be held in abeyance.

Information Disclosure Statement

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 or applicant on form PTO-1449 have cited the references they have not been considered.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The term "of less than about" in claim 16 is a relative term which renders the claim indefinite. The term "less than about" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear if applicant intends to claim compositions< and = to 5000 Dalton or only compositions <5000 Dalton.

Applicant argues that the claim clearly refers to molecules having a molecular weight that is less than or equal to 5000D, and that in light of the specification one of skill in the art would know that the claim covers the use of an equivalent small molecule that might slightly exceed about 500D in weight, so long as the molecule would still be considered small and not substantially different from molecules following within the literal range. This argument was carefully considered but not found persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The mere reference to a molecular weight "of less than about" or slightly exceeding 5000D without clearly defining (what would be considered substantially different) does not clearly provide a standard for ascertaining the inventive molecule. The rejection is maintained.

D. Claim 16 recites the limitation "an effective amount". The phrase remains indefinite when the claim fails to state the function which is to be achieved. Although the claim recites the inhibition of a binding event, because the detection of such inhibition has not been clearly defined by the claims (including essential method steps) the intended function is not known. *In re Frederiksen,* 213 F 2d 547, 102 U.S.P.Q. 35 (C.C.P.A. 1954).

Applicant argues that the method in a host (in vivo) has no missing steps. However, it is noted that the method does not include a separation step, a detection step wherein the complex formed in vivo will be identified to allow for correlation of bonding inhibition. An assay or method, as proposed in the preamble of claim 16, require at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step

E. Claim 16 remains vague and indefinite because it is unclear as to how binding inhibition will occur. Although the claim recites an interaction between a first target protein and a second binding protein in a host, the method does not clearly outline how the second protein and blocking protein interact such that inhibition of the first and second is accomplished. The claims merely read on the formation of a tripartic complex comprising the bifunctional inhibitor molecule, the target protein, and the blocking protein. But does not identify the correlation/interaction/detection allowing for comparative analysis between this tripartic complex and the second binding proteins inhibition. Will the blocking protein and second binding protein compete for the same binding site on the target protein therein allowing for measurement of the blocking protein as an inverse measure for the second binding protein. The method does not including essential method steps.

Applicant argues that the claims are not indefinite in light of the specification. Wherein the specification clarifies that the tripartite complex prevents access of the second protein to its binding site on the target protein. This argument was carefully considered but not found persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

9. Claims 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are elucidated below:

Independent claims 1 is drawn to a method inhibiting a binding event between a first target protein and a second binding protein in a host. Merely reciting a method including the reagents, is not considered to be a proper method (including all the required method steps). Although the specification teaches methods on pages 20-21, the claims do not include the essential method steps. An assay or method, as proposed in the preamble of claims 1, require at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step. These essential steps for the method have not been outlined for determining protein-protein interaction inhibition. It is suggested that Applicant add steps that at least reflect: (I) a sample and reagent contacting step, (II) the binding or complex formation of a labeled product, the detection of the labeled product, and (III) a correlation step. Please include the necessary steps.

Applicant argues that the method in a host (in vivo) has no missing steps. However, it is noted that the method does not include a separation step, a detection step wherein the complex formed in vivo will be identified to allow for correlation of bonding inhibition. An assay or method, as proposed in the preamble of claim 16, require at least a contact step between reagents and sample, the separation of unbound and bound material, a detection step, and a correlation step

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

I. Claims 16-24 are rejected under #35 U.S.C. 102(b) as being anticipated by Griffith et al. (Cell, Vol.82, pages 507-522, August 11, 1995).

Griffith et al. disclose the ternary complex of calcineurin A fragment, calcineurin B, FKBP12, and the immunosuppressant drug FK506. The ternary complex provides a structural basis for understanding calcineurin inhibition by FKBP12-FK506. See abstract. The reference meets applicants claimed limitations by teaching the same reagents disclosed in the experimental design present on pages 20-21. The FKBP12-FK506 complex inhibits calcineurin phosphatase activity by blocking the active site from macromolecular phosphorylated substrates like NF-ATp. The information is further taught to be applicable as therapeutic inhibitors. Page 518, Conclusion.

Response to Arguments

Applicant argues that the bifunctional molecule employed in the subject claims is a non-naturally occurring molecules and FK506 utilized in Griffith et al. is naturally occurring. This argument was carefully considered but not found persuasive because Griffith et al. disclose a bifunctional complex FK506-FKBP12 formed from recombinant means. See abstract and page 519, 1st column, 2nd paragraph.

Further the instant invention employs complexes that include FK506. Please see the specification page 15 line 6-23. The rejection is maintained.

II. Claims 16-21 and 24 are rejected under #35 U.S.C. 102(b) as being anticipated by Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998).

Varshavsky teaches multitarget compounds specific for negative targets concerning the concept of codominant interference. The reference discloses compositions linking two small moiety ligands (< 1Kd page 2095) bipartite compounds consisting of two ligands bound together by a linker (1* and c in Fig. C and D). The ligands are capable of simultaneously binding target protein (C in figure D) and blocking proteins (1 in figure C) thereby possibly forming a tripartite complex. Multitarget drugs designed according to the specific configurations taught by Varshavsky were taught to be useful in the selective killing of cancer cells via the inhibition of a neurotransmitter-inactivating enzyme in a specific subset of the enzyme-containing cells. Therein teaching protein-protein inhibition. See abstract.

Response to Arguments

Applicant argues that the Varshavsky et al. do not show the production of tripartite complexes (combination of three distinct molecules) and further teaches away from the instant invention because Varshavsky's scheme only works if the bifunctional molecule cannot form a tripartite complex with a target protein and blocking protein. This argument was carefully considered but not found persuasive because Varshavsky et al. disclose a tripartite complex compound abi – see figure 1.

Varshavsky et al. also discuss method of inhibiting the binding of a second target protein. Support for this assertion is seen in figure 2 wherein the I moiety of the abi compound inhibits an essential enzyme I. Therefore the rejection is maintained.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Varshavsky (Proc. Natl. Acad. Sci. USA Vol.95, pp. 2094-2099, March 1998)in view of Pouletty et al. (WO 95/10302).

Please see previous discussions of Varshavsky as set forth above.

Varshavsky differ from the instant invention in failing to teach tripartite complexes produced extracellularly.

However, Poulett et al. teach bifunctional reagents useful in extending in vivo lifetimes of physiologically active agents further reducing the biologically effective concentration or activity of an endogenous or exogenous blood component. Page 2, lines 14-20. A target binding member, which is a physiologically active agent in a mammalian host is bound to a protein via a reagent or conjugate possibly including a linking group. See pages 19 and 20. Applicable proteins include albumin, transferrin, ferritin, and immunoglobulins. See page 3, lines 5-25. The second binding member is usually a macromolecule of at least 5000 Dalton. Page 25, lines 20-25. The bifunctional reagents are taught to have utility in therapeutic methods to detect host derived and foreign targets. Page 5, lines 6-10.

Varshavsky and Poulett et al. are analogous art because they are from the same field of endeavor, both inventions teach techniques involving bifunctional reagents.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the proteins endogenous to the host (i.e. albumin, vitamin receptor, etc..) as taught by Poulett et al. in the method of Varshavsky to perform protein-protein inhibition assay techniques, because such endogenous proteins as taught by Poulett et al. are well known in the art. A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such endogenous proteins, because Poulett et al. taught that the selected blocking protein (long-lived blood component) would affect the manner in which the biological activity of the target is modified and the selection will vary dependent on the nature of the target.

Page 30, lines 23-30. In other words compounds endogenous to the host would cause less side effects and extend dosage levels. Page 1, lines 26-30.

One having ordinary skill in the art would have been motivated to do this because the blocking protein can impart its physiological activities to the target binding member. In this way cellular targets may be inactivated or eliminated. Page 33, lines 16-22.

Response to Argument

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, blocking proteins can impart physiological activities to the target binding member. In this way cellular targetes may be inactivated or eliminated. Poulett et al., page 33, lines 16-22.

12. For reasons aforementioned, no claims are allowed.

13. This action is made NON-FINAL.

Remarks

14. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Weiderrecht et al. (U.S. Patent#5,457,182) teach binding interactions involving FK-506 and FKBP12.6.

B. Maragarnore et al. (U.S.Patent#5,242,810) disclose bifunctional inhibitors of platelet activation and thrombin.

15. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
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5/1/02

CHRISTOPHER L. CHIN
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